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Photoorganocatalytic α-oxyamination of aldehydes

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Dedicated to Prof. Jacek Młochowski on the occasion of his 80th anniversary

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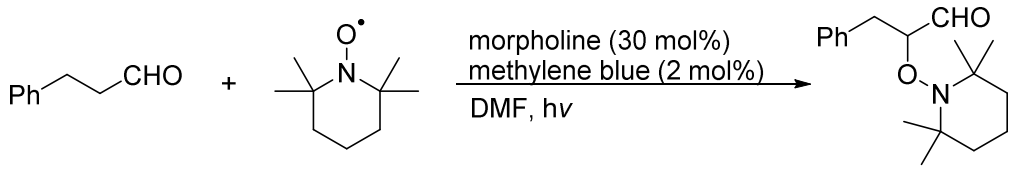
Abstract

Methylene blue catalyzes the visible light-induced organocatalytic α-oxyamination of aldehydes via enamines. The irradiation of 3-phenylpropanal with TEMPO radical in the presence of morpholine as an organocatalyst and methylene blue as a photoredox catalyst gave the desired α-functionalized aldehyde in 75% yield.



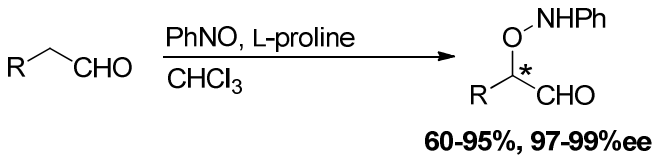
Keywords: Photoredoxcatalysis, oxyamination, aldehydes, enamine, organic dyes, visible light

Introduction

Over the years various methods for the introduction of both protected and unprotected hydroxy groups in close proximity to the carbonyl functionality have been developed. Particular attention has been paid to the functionalization of aldehydes at the α-position as the resulting α-hydroxyaldehydes are very reactive species hence allowing for subsequent elaboration.[1]

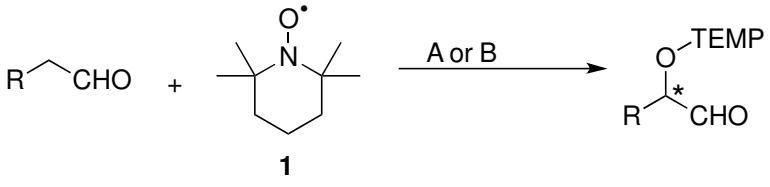
In this regard, the organocatalytic reaction of aldehydes with photochemically generated singlet oxygen seems the most straightforward and green option.[2-4] Using this methodology various α-hydroxyaldehydes were obtained in reasonable yields. Very often, after in situ reduction they were transformed into desired diols - (*S*)- or (*R*)- depending on the catalyst used. (*S*)-Enantiomer predominated in imidazolidinone-catalyzed reactions, while prolineamides assured the formation of (*R*)-stereoisomer. However, in depth studies, revealed that an enamine generated from an aldehyde and an organocatalysts could be oxidized thus diminishing the yield of the desired product.[5,6]

On the other hand, the MacMillan's group exploited nitrosobenzene as an oxidant. In these of recently organocatalyzed reactions of aldehydes with nitrosobenzene, α-oxyaminated products formed in good yield and excellent enantioselectivity (Scheme 1).[7] But carcinogenity of nitroso compounds cannot be ignored, thus limiting the applicability of the developed method, especially in the pharmaceutical industry. The same can be said about organocatalytic α-oxidation of aldehydes with hazardous benzoyl peroxide leading to α-benzoyloxyaldehydes, though valuble oxidized products were obtained in good yields and excellent enantioselectivities using imidazolidinone[8], dipohenylprolinol silyl ether[9] or diphenylmethyl pyrrolidine[10] as organocatalysts.



Scheme 1. α-Oxidation of aldehydes with nitrosobenzene.

In 2007 Sibi *et al.* reported an alternative method for the synthesis of α-oxyaminated products using stable 2,2,6,6-tetramethylpiperidine-1-oxyl radical (TEMPO, **1**).[11] Only in the presence of imidazolidinone tetrafluoroborate, $FeCl_3$, and $NaNO_2$ did products form in good yield and stereoselectivity (Scheme 2, A). The formation of an iminium radical cation from an enamine via a SET process was proposed but further mechanistic studies revealed that in fact $FeCl_3$ promotes an electrophilic attack of the TEMPO-$FeCl_3$ complex on an enamine acting only as a Lewis acid.[12] Based on the proposed mechanism, the formation of TEMPO-$FeCl_3$ complex, developed by the MacMillan's group, more general conditions for the Sibi oxyamination were evolved. It was found that the replacement of $FeCl_3$ with $CuCl_2$ that formed stable complexes with TEMPO, provided functionalyzed aldehydes in high yield and ee up to 93%. Later, Koike and Akita expanded this methodology by performing this reaction in a photocatalytic manner.[13] Under light irradiation $[Ru(bpy)_3](PF_6)_2$ catalyzed oxidative coupling of an enamine, generated in situ from an aldehyde and morpholine, with TEMPO affording desired products in reasonable yields. The proposed mechanism assumed the coupling of TEMPO radical (**1**) with an iminium radical cation, generated via the reaction of enamine with the *Ru(II) complex (Scheme 2, B).



A) Sibi *et al*[11]
1. imidazolidinone HBF_4
$FeCl_3$, $NaNO_2$, O_2, DMF
2. $NaBH_4$
49-80%, 0-90%ee

B) Koike and Akita[13]
morpholine
$[Ru(bpy)_3](PF_6)_2$, h*v*, CH_3CN
45-68%

Scheme 2. α-Oxyamination of aldehydes with TEMPO.

The first light-induced, enantioselective oxyamination of aldehydes was reported by Jang and co-workers. The use of heterogenous TiO_2 in place of $Ru(bpy)_3(PF_6)_2$ assured the formation of α-functionalized aldehydes in a moderate yield and enantioselectivity. Under the developed conditions derivatives of prolinol outperformed imidazolidinones as a source of chirality.

To date, transition metal complexes are the most popular photoredox catalysts in visible light driven functionalization of aldehydes.[14,15] Recently, however, it was shown that in certain cases, simple and inexpensive organic dyes could be used as photoredox catalysts, thus making the processes greener and more suitable for large scale pharmaceutical production.[16] For example, Zeitler *et al.* performed organocatalytic α-alkylation of aldehydes in the presence of eosin Y, which originally exploited $Ru(bpy)_3Cl_2$,[17] giving the desired products with similar yields and enantiomeric excesses.[18] *Hence, we envisaged that the visible-light driven oxyamination reaction described could be realized with organic dyes eliminating the need for the use of precious metal complexes.*

Results and Discussion

In a preliminary experiment 3-phenylpropanal (**2**) was reacted with TEMPO radical (**1**) in the presence of morpholine and $Ru(bpy)_3Cl_2$ under white light irradiation for 16 h (Table 1, entry 1). The reaction afforded desired product **3** in only 30% yield. The yield significantly increased to 71% when CH_3CN was replaced with DMF (entry 3). Due to incomplete conversion of the starting materials, the reaction was prolonged giving a decrease in yield (entry 4). The same results were obtained either with the addition of an excess of TEMPO (**1**) or 1,3-dinitrobenzene as a sacrificial electron donor (entries 6 and 7).

The next step involved the use of chiral secondary amines in place of morpholine. Contrary to the reaction in the presence of TiO_2, – L-proline and its derivatives **4**, **5**, **6** and imidazoline (**7**) catalyzed reactions were unselective (*ee* 0%) and low yielding (entries 8-10).

Examination of organic dyes as photoredox catalysts gave a surprising result. Eosin Y (**9**), which is often readily substituted by a ruthenium complex in α-alkylation reactions, proved to be inefficient in the present context (Table 2, entry 1). The use of rose Bengal (**10**) which was successfully used in α-oxyamination of aromatic β-ketoesters,[19] gave only traces of product **3** (entry 2). Interestingly, optimum result was achieved in the reaction catalyzed by methylene blue (**13**) (entry 5).

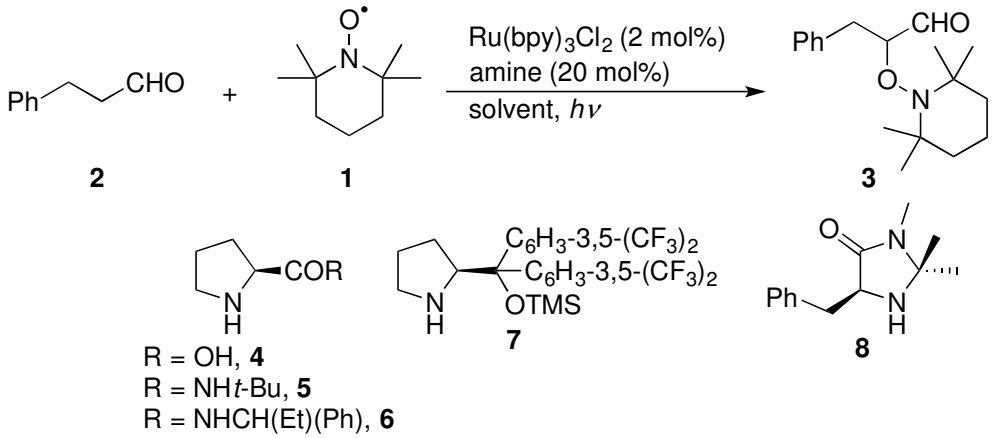
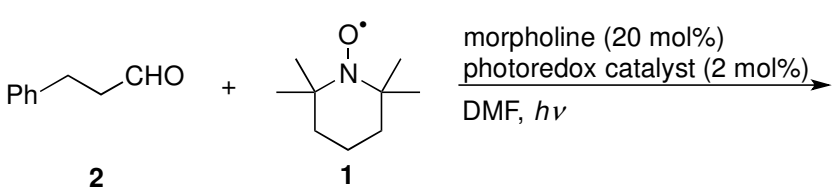


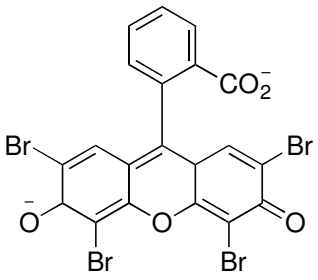
Table 1. Short optimization of $Ru(bpy)_3Cl_2$ catalyzed α-oxyamination of aldehydes

Entry	Solvent	Amine	Time (h)	Yield (%)[a]
1	CH_3CN	morpholine	16	30
2	DMSO	morpholine	16	44
3	DMF	morpholine	16	71
4	DMF	morpholine	24	39
5	DMF	morpholine	1	trace
6	DMF	morpholine	16	46
7[b]	DMF	morpholine	16	53
8	DMF	imidazoline **8**	16	trace
9	DMF	L-proline **4**	16	20
10	DMF	prolinol **7**	16	22

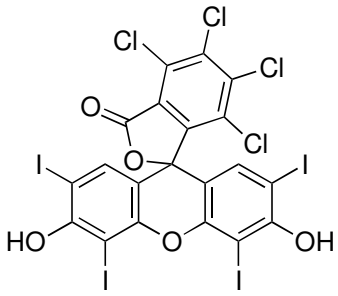
Reaction conditions: [a]3-phenylpropanal (**2**, 1 mmol), TEMPO (**1**, 1 mmol), secondary amine (0.2 mmol) and $Ru(bpy)_3Cl_2$ (2 mol%) in 10 mL of solvent, irradiated for a specified amount of time by 2 white 4 W "household" LED bulbs. [b]Reaction performed with addition of 1 equiv. 1,3-dinitrobenzene.



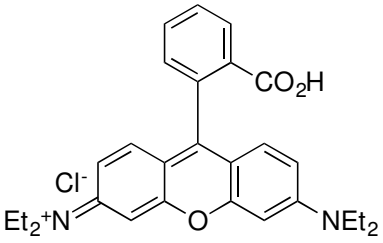
2 **1** **3**



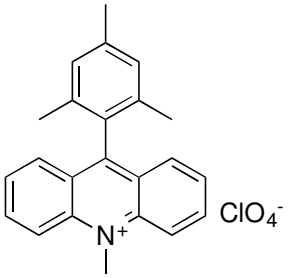
Eosin Y (**9**)



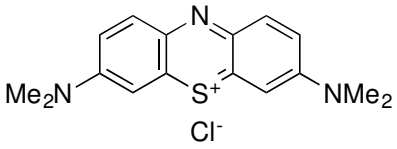
Rose Bengal (**10**)



Rhodamine (**11**)



10-Methyl-9-(2,4,6-trimethylphenyl)acridinium (**12**)



Methylene blue (**13**)

Table 2. Screening of suitable photoredox catalysts

Entry	Photoredox catalyst		Yield (%)[a]
1	eosin Y	(**9**)	0
2	rose Bengal	(**10**)	7
3	rhodamine B	(**11**)	20
4	10-methyl-9-(2,4,6-trimethylphenyl)acridinium	(**12**)	13
5	methylene blue	(**13**)	68

Reaction conditions: [a]3-phenylpropanal (**1**, 1 mmol), TEMPO (**2**, 1 mmol), morpholine (0.2 mmol) and photoredox catalyst (2 mol%) in DMF (10 mL), irradiated for 16 h by 2 white 4 W "household" led bulbs.

After successful implementation of methylene blue, further optimization of the reaction conditions with respect to reaction time, solvent, light, and the amount of morpholine were performed (Table 3). CH_3CN assured the highest reaction yield within only 5 h reaction time (entry 3). Unfortunately, the pyrrolidine-catalyzed reaction furnished product **3** in a lower yield than the morpholine-catalyzed process, opposite to most of enamine-iminium catalyzed reactions (entry 4).[20] Better results generated prolinamides **5**, **6** and though no selectivity was observed (entries 5, 6). In the final step LED bulbs were replaced with white LEDs leading to a futher increase in the yield <75%.

Table 3. Screening of suitable photoredox catalysts

Entry	Secondary amine	Solvent	Light source	Time (h)	Yield (%)[a]
1	morpholine (40 mol%)	DMF	2 LED bulbs	16	68
2	morpholine (30 mol%)	DCM	3 LED bulbs	5	40
3	morpholine (30 mol%)	CH_3CN	3 LED bulbs	5	72
4	pyrrolidine (30 mol%)	CH_3CN	3 LED bulbs	0.25	trace
5	prolinamide **5** (20mol%)	CH_3CN	3 LED bulbs	3	38
6	prolinamide **6** (20mol%)	CH_3CN	3 LED bulbs	3.5	59
7	morpholine (30 mol%)	CH_3CN	Green LED	5	40
8	morpholine (30 mol%)	CH_3CN	White LED	5	75

Reaction conditions: [a]3-phenylpropanal (**1**, 1 mmol), TEMPO (**2**, 1 mmol), amine (0.2 - 0.4 mmol) and methylene blue (2 mol%) in 10 mL of solvent, irradiated for specified amount of time by 2 white 4 W "household" led bulbs, each 300 Lumens.

Under optimal conditions various aldehydes were reacted with TEMPO (**1**) (Chart 1). Even though the list of aldehydes is not extensive, it is representative. All tested aldehydes, except α-branched one, provided α-oxyaminated aldehydes in reasonable yields. It is known that the formation of a quaternary stereogenic centre may be problematic, thus further optimization studies were performed for this class of aldehydes. Even, 2-hexen-1-al transformed into α,β-unsaturated product (**19**). This example shows that the oxyamination of carbonyl compounds can proceed not only via an enamine but also via dienamine-catalysis, a much more demanding process.

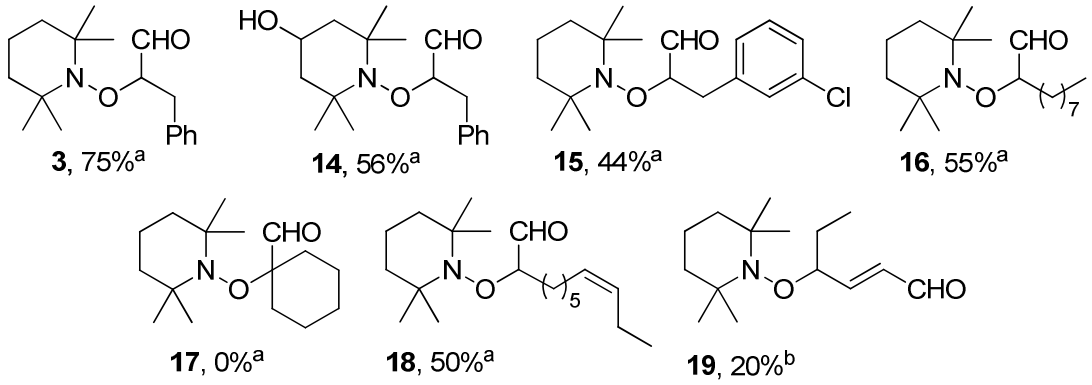


Chart 1. α-Hydroxylated aldehydes – scope and limitations of the developed method.
Reaction conditions: [a] Aldehyde (1 mmol), TEMPO (**1**, 1 mmol), morpholine (0.3 mmol) and methylene blue (2 mol%) in CH_3CN (10 mL), irradiated for 5 h by white LEDs. [b] Aldehyde (1 mmol), TEMPO (**2**, 1 mmol), morpholine (0.3 mmol) and methylene blue (1 mol%) in CH_3CN (10 mL), irradiated for 1 h by 4 white 4 W household led bulbs.

It is worth mentioning that an unsaturated aldehyde gave the desired product with no oxidation of the double bond being observed. This result opens possibilities for further functionalizations of such compounds via epoxidation, dihydroxylation, aminohydroxylation, etc.

Conclusion

We have found that the organocatalytic α-oxyamination of aldehydes can be performed under light irradiation not only in the presence of Ru-complexes but also using methylene blue as a photocatalyst. Under the developed conditions α-oxyaminated products were obtained in decent yields, but enantioselectivity requires further scrutiny. Interestingly, even unsaturated aldehyde gave the desired product with no oxidation of the double bond being observed.

Experimental Section

General. ^{1}H and ^{13} C NMR spectra were recorded at rt on Bruker 400 and Varian 600 MHz instruments with TMS as an internal standard. The chemical shifts (δ) and coupling constants (*J*) are expressed in ppm and Hertz respectively. Thin layer chromatography (TLC) was performed using Merck Silica Gel GF254, 0.20 mm thickness. All solvents and chemicals used in the syntheses were of reagent grade and were used without further purification. High resolution ESI mass spectra were recorded on a Mariner and SYNAPT spectrometer. Aldehydes were purified by flash column chromatography (hexane: AcOEt) if necessary. Photo-induced reactions were performed using a homemade photoreactor equipped with four LED light bulbs (with 4 W 'household' bulbs 1200 Lm; warm light).

Procedure for α-oxyamination of aldehydes. Photocatalyst (2 mol%) was placed in a reaction tube and dissolved in CH_3CN (10mL) under argon. Then TEMPO (1 equiv., 1 mmol), aldehyde (1 mmol) and morpholine (0.3 equiv., 0.3 mmol) were added to the solution. The reaction mixture was stirred under irradiation (white LEDs) for 5 h. The light was turned off and the reaction mixture was concentrated. The crude product was purified by flash chromatography using silica gel (hexanes/AcOEt) to afford the corresponding product.

3-phenyl-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)propanal[21] (**1**) (colourless oil, 220 mg, 75%).
2-((4-hydroxy-2,2,6,6-tetramethylpiperidin-1-yl)oxy)-3-phenylpropanal (**10**). (pale yellow oil, 172 mg, 56%) R_f = 0.28 (6:4 hexane:AcOEt). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.78 (1H, d, *J* 4.4Hz), 7.31-7.18 (5H, m), 4.39-4.30 (1H, m), 3.98-3.88 (1H, m), 3.12- 2.93 (2H, m), 1.83-1.72 (2H, m), 1.48-1.38 (2H, m), 1.15 (6H, s), 1.13 (6H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ_c 203.7, 135.9, 129.9, 128.6, 128.6, 126.9, 88.6, 60.6, 36.9, 21.2, 14.4.
3-(3-chlorophenyl)-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)propanal (**11**). (pale yellow oil, 154 mg, 47%) R_f = 0.46 (9:1 hexane:AcOEt). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.82 (1H, d, *J* 4.2Hz), 7.24 (1H, d, *J* 4.6Hz), 7.23-7.18 (2H, m), 7.12-7.06 (1H, m), 4.37-4.32 (1H, m), 3.28-2.66 (2H, m), 1.51-1.24 (6H, m), 1.13 (6H, s), 1.10 (6H, s). ^{13}C NMR (101 MHz, $CDCl_3$) δ_c 203.9, 138.3, 134.3, 130.1, 129.7, 128.1, 127.1, 88.1, 40.3, 36.5, 17.3. HRMS calcd for (M+MeOH, hemiacetal) $C_{19}H_{31}NO_3Cl$ 356.1996; found 356.1992 (-0.3 ppm)
2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)decanal (**12**).[22] (colourless oil, 171 mg, 55%).
(*Z*)-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)undec-8-enal (**14**). (colourless oil, 162 mg, 50%) R_f = 0.71 (9:1 hexane:AcOEt). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.77 (1H, d, *J* 4.5Hz), 5.40-5.26 (2H, m), 4.16-3.99 (1H, m), 2.07-1.97 (4H, m), 1.77-1.60 (2H, m), 1.47-1.40 (4H, m), 1.39-1.27 (8H, m), 1.16 (6H, s), 1.13 (6H, s), 0.95 (3H, t, *J* 7.5Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ_c 204.8, 131.9, 129.2, 88.7, 40.3, 30.2, 29.6, 29.5, 27.1, 24.4, 20.7, 17.3, 14.6. HRMS calcd for (M+MeOH, hemiacetal) $C_{21}H_{42}NO_3$ 356.3177; found 356.3165 (-1.2 ppm)
(*E*)-4-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)hex-2-enal (**15**).[23] (colourless oil, 51 mg, 20%).

Acknowledgements

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